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Physiological Activities of Certain Glycol Derivatives

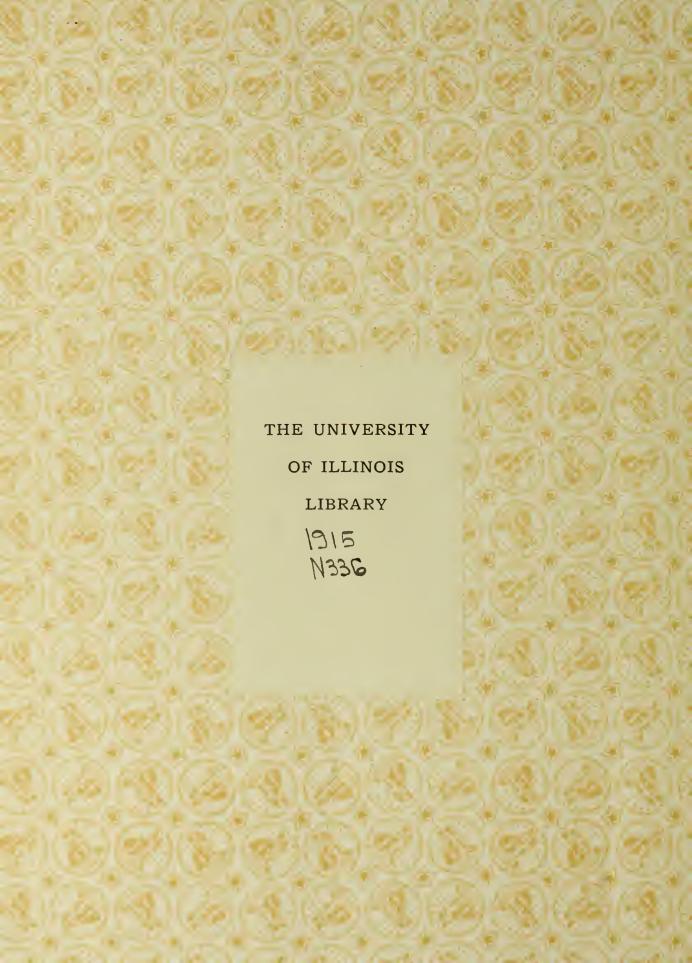
Chemical Engineering

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1915



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# PHYSIOLOGICAL ACTIVITIES OF CERTAIN GLYCOL DERIVATIVES

 $\mathbf{BY}$ 

### RALPH AUGUSTUS NELSON

# THESIS

FOR THE

DEGREE OF BACHELOR OF SCIENCE

IN

CHEMICAL ENGINEERING

COLLEGE OF LIBERAL ARTS AND SCIENCES

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1915



## UNIVERSITY OF ILLINOIS

May 25 " 1915

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY RALPH AUGUSTUS NELSON

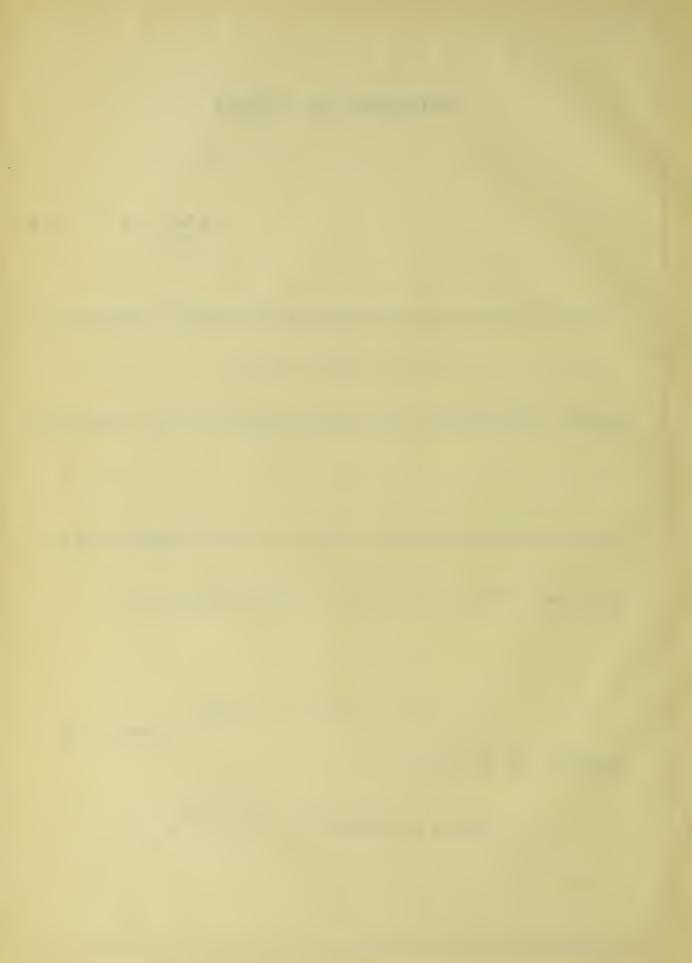
ENTITLED PHYSIOLOGICAL ACTIVITIES OF CERTAIN GLYCOL DERIVATIVES

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemical Engineering

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HISTORICAL

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INTRODUCTION.



PHYSIOLOGICAL ACTIVITIES

OF

CERTAIN GLYCOL DERIVATIVES.

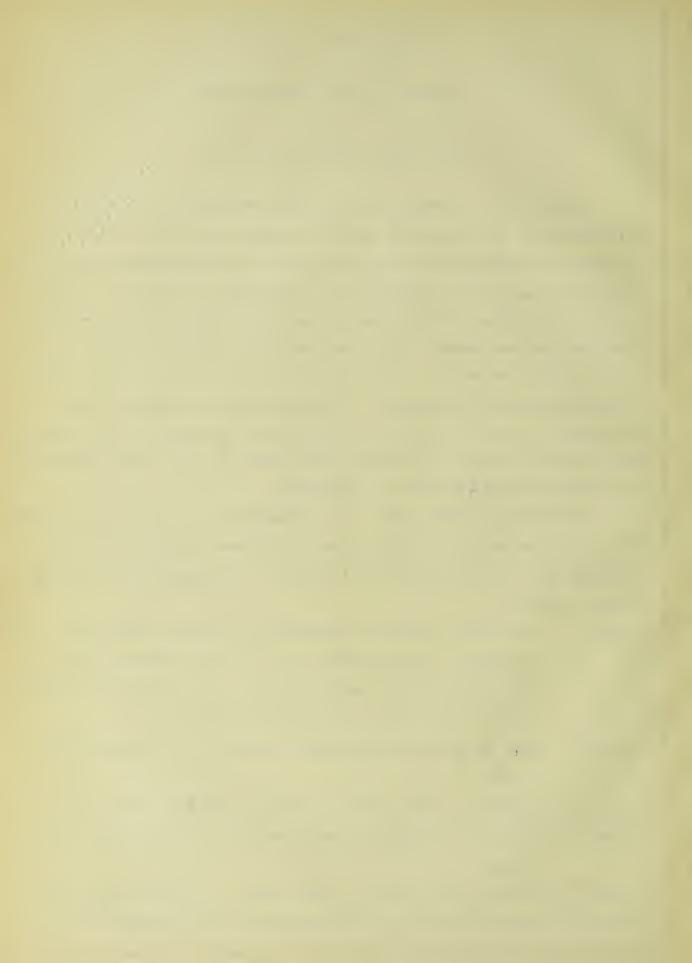
### HISTORICAL AND INTRODUCTION.

Soporifics or narcotics have the same general action as anaesthetics, but are only used to produce the first effects of imperfect consciousness. The action of the anaesthetic persist but a short time, while the narcotic is required to produce a slight but lasting effect. The anaesthetics are volatile bodies rapidly absorbed and excreted. Hypnotics are less volatile liquids or solid substances whose activity is but gradually released in the organism producing hypnosis. The physiological action of the aliphatic narcotic is first on the higher centres of the cerebrum and then on the lower centres of the medulla and cord. Eventually the reflexes are completely abolished.

Overton, on the basis of his researches on the velocity with which substances diffuse into the protoplasm, divides these substances into the following four classes according to the rate of their diffusion.

- Class I. Univalent alcohols, aldehydes, ketones, aldokimes, and ketoximes, nitro-alkyl and cyanides, neutral esters of the inorganic and many organic acids, aniline, pyridine.

  and the majority of free alkaloids.
- Class II. The divalent alcohols and amides of mono-carboxylic acids.
- Class III. Glycerol, urea, the hexoses and amido-acids.
- Class IV. Salts of strong inorganic acids, inorganic acids and bases.
- Class I diffusing most rapidly, and class IV contains those substances to which the cells are impermeable. The permeability



increases in homologous series.

In general this rate of diffusion is coordinated with the solubilities of these substances in such substances as fats and cholesterin, and Overton advances the hypothesis that the magnetude of the distribution coefficient between fat and water determines the velocity of osmosis. Both Overton and Meyer point out that as a rule narcotics diffuse rapidly, and draw the conclusion, that the narcotic value of a compound depends principally on its solubility in the lipoid substances. No direct relationship is found between the solubilities in vater and the narcotic power.

The Overton-Meyer theory then is that the hypnotic gains access into the cell due to its solubility in the cell lipoids, and that the different degrees of activity of the different hypnotics are due to the presence of groups which increase the partition coefficient rendering the derivative more soluble in the lipoid substances.

Traube differs from Overton as to the manner in which the substances enter the cell, believing that it is not the amount of lipoid which determines the velocity of osmosis, but that this is due to the differences in surface tensions. He finds a near relation between surface tensions and osmotic velocity, and likewise that surface tension and narcotic power run parallel. He considers that after the drug is in the cell its narcotic power is proportional to its solubility in the cell lipoids.

The work of Moore and Roaf seems to indicate that adsorption constitutes the mechanism by which the narcotic is taken up in the cell.

These theories only explain the presence of the active substance in the cell, but we are in ignorance as to how they act in producing narcosis. Baglioni, basing his conclusions on obser-



vations on the various benzene phenol derivatives, has formulated the hypothesis that narcosis is a reducing process, that the narcotic effect depends on the power of the drug to withdraw oxygen from the 'inogen' compounds in the central nervous system.

Judging from the large number of substances belonging to the methane series that produce narcosis it seems that this characteristic combination of carbon and hydrogen combined in open form chain is possessed of specific depressant values. Though methane is not a narcotic, etnane and acetylene are direct narcotics. As a general rule the greater number of these carbon radicals contained in the chain, the more powerful the action, provided the substance is not changed so as to become incapable of absorption.

Hypnotics include those of

- I. The chloral hydrate group. e.g. chloral. To this group belong also chloralamide and paraldehyde.
- II. The tertiary amyl alcohol class, characterized by the presence of a hydroxyl and a carbon united to three alkyl groups. e.g. amylene hydrate.
- III. The intermediate dormiol class. e.g. tertiary amyl chloral.
- IV. The urethane derivatives. e.g. urethane, hedonal.
- V. A group of compounds containing a single carbon united to
  two alkyl groups and two sulphonic residues.
  e.g. sulphonal, trional.
- VI. A group of compounds studied by E. Fischer and consisting of derivatives of urea. e.g. veronal.

Analysis of these groups show them to be alcohols, aldehydes, ketones or their derivatives, or urea derivatives.

The hypnotics belonging to the alcohol group owe their activity to the hydrocarbon radical. An increase in the number of hydroxyl groups present in the molecule causes a decrease in



the physiological activity. An increase in molecular weight, increasing as the homologous series ascends, is followed with an increase in narcotic power. The primary alcohols are less narcotic than the secondary, and these less than the tertiary.

Of the ethers (which may be considered alcohol derivatives) ethyl ether is probably our best anaesthetic. Increase in molecular weight of the ethers brings about a decrease in the physiological activity. The mixed aliphatic ethers have not been investigated.

The aldehydes and ketones, as a rule are not convenient narcotics, as they cause a preliminary stage of excitement and are ordinarily irritant. Many of the aldehyde derivatives unsubstituted by halogens are but feebly narcotic. Excepting the sulphones the ketones do not yield any bodies of importance.

In the sulphones, and also in the urea and the urethane derivatives, again is seen the striking effect of increased physiological activity by the substitution of the ethyl group for the methyl group.

The entrance of carboxyl into the compound appears to stop all narcotic effects; but the alkyl esters are again active, the activity likewise increasing the higher the molecular weight of the alkyl group replacing the hydrogen of the carboxyl radical.

Some of the most important members of this series are the halogen substitution products. The introduction of halogen, more especially chlorine, into the molecule enhances very (reatly the narcotic power; but, at the same time, it also increases their activity as cardiac and respiratory depressants.

In proceeding with this work, the jurpose has been the study of the effect of the ether grouping in the molecule which already contains an hydroxyl group, since the ether residue is



well known to have marked narcotic properties, as is evidenced in urethane and other. Also the original idea was to prepare a compound that would combine hypnotic activity with ready solubility. The alcohol selected for the work was a mono ethyl other of a disubstituted ethylene glycol. This alcohol was prepared by means of the Grignard synthesis from ethylbronide and ethoxyacetic ester:

This tertiary alcohol was converted into the bromoacetyl derivative by the direct action of bromoacetylbromide:

 $C_2 H_5 OCH_2 C(OH) (C_2 H_5)_2 + BrCOCH_2 Br = C_2 H_5 OCH_2 C(C_2 H_5)_2 OOCCH_2 Br + Her$  and this ester by the action of diethylamine was converted into the diethylamino derivative:

 $C_2H_5OCH_2C(C_2H_5)_2OOCCH_2B_T + HN(C_2H_5)_2$ 

$$= C_2 H_5 OCH_2 C (C_2 H_5)_2 OOCCH_2 N (C_2 H_5)_2$$

This base should form soluble salts which would facilitate subcutaneous administration; but, unfortunately, the hydrochloride was extremely hydroscopic, and therefore difficult to handle. The tertiary alcohol was found to have marked hypnotic properties, tests with it being made on a dog.







Ethyl Ester of Chloroacetic Acid.

Two hundred grams of chloroacetic acid, 200 grams of alcohol and 30 grams of conc. sulphuric acid were placed in a flask and refluxed for four hours over a small flame. The excess of alcohol was then distilled off, the residue poured on cracked ice and then neutralized with sodium carbonate. This solution was extracted with ether and the ether extract dried over calcium chloride. Upon distillation the ester came over at 141° - 142° (uncor.) Yield 75 to 80 percent.

Ethyl Ester of Ethoxyacetic Acid.

Sodium ethylate was prepared using 24 grams of sodium and 250 c.c. of absolute alcohol. To the cooled product 120 grams of the chloroacetic ethyl ester were added slowly and with shaking. The reaction was very vigorous and it was found necessary to cool the flask several times under the faucet during the addition. To complete the reaction the mixture was finally heated one hour on the water bath. The alcohol was distilled off by means of an oil bath, and after the addition of 300 c.c. of water the solution was extracted three times with ether. The ether extract was dried over calcium chloride and upon distillation the distillate coming over between 145° - 165° was collected. This was fractionated and the product coming over between 153° - 158° was taken. The product in the main came over at 155°. Yield approximately 75 percent.



Ethoxy-Methyl-Diethyl Carpinol.

For the preparation of this alcohol the Grignard synthesis was made use of. Twenty one and a half grams of cleaned magnesium ribbon were placed in a flask, covered with 250 c.c. of dry ether and the flask connected to a reflux condenser. To this 50 grams of ethyl bromide were acded. After practically complete solution of the magnesium, 52 grams of the ethoxyacetic ethyl ester, dissolved in an equal volume of dry ether, were added to the cooled solution. The reaction was very vigorous, forming at first an insoluble addition product which upon shaking went into solution. It was found advantageous to keep the mixture in a cooling path at a temperature of about 30°. The mixture was finally heated one half hour on the water bath. It was then cooled and cracked ice added gradually to break down the addition product. The preciptated magnesium hydroxide was dissolved by addition of conc. HCl. the ether layer separated and dried over fused potassium carbonate. Upon distillation the tertiary alcohol came over between 162-16°. The alcohol has a pleasant pepermint like odor and is but very slightly soluble in water. Yield 90-95 percent.

Bromoacetic Ester or Sthowy-Methyl-Diethyl Carbinol.

This product was prepared by the direct action of bromoacetyl bromide on the tertiary alcohol. Very good yields of the
condensation product were not obtained. The condensation was
tried in the medium dry ether but the reaction was very slow
requiring heating for a long period on the water bath. Without
the presence of ether the reaction was more rapid, but on heating
on the water bath the solution became very dark in color suggesting that the HBr formed caused a breakdown of the molecule.
Hence the reaction was repeated in the presence or calcium



carbonate using just a small amount of ether. In this case the darkening was not observed. Twenty five to forty grans of the product were obtained from thirty grans of the alcohol. The best results were obtained in the presence of ether alone.

At completion of the reaction the product was poured into ice, and then made alkaline with slight excess of sodium carbonate. The ester layer was separated and washed with water, and the water extracted once with ether. The ether extract was dried over calcium chloride and the product then distilled in vacuo. The product did not come over constantly, the temperature ranging from 60°-80° under 25-35m.m. pressure. The ester is a clear colorless liquid, insoluble in water, but soluble in the comon organic solvents.

Diethyl Aminoacetic Ester of Etnoxy-Methyl-Diethyl Carolnol.

The diethyl amine used in the preparation of this base was made from diethylaniline through the nitroso compound by the action of caustic soda, according to the method of Norris and Kimperiy. (1)

Two mols of diethyl amine were condensed with one mol of the ester. The diethyl amine was added to a solution of the bromo derivative in dry ether. Immediately white silky like fluculent crystals began to separate out. After standing sometime, dilute HCl was added, the mixture shaken well, and the two layers separated. The water solution contained the hydropromide and the hydrochloride salts of the product and of the extra mol of diethyl amine. The solution was made alkaline with conc. AOH, extracted with ether, and the ether extract dried over fused potassium carbonate. The product was distilled in vacuo, and came over fairly constantly at apposimately 63° at about 25 m.m. pressure, or around 100° at 40 m.m. pressure. A yield of 30 grams 1. Am. Chem. Jour. 20, 660, 1898.



was obtained from 40 grams of the bromo derivative. The product freshly prepared is a colorless liquid.

The hydrochloride of this base was prepared and found to be extremely deliquescent.

Analysis for nitrogen was made by the Kjeldahl nethod.

Analysis:

Diethyl aminoacetic ester of

ethony-methyl-diethyl carbinol. sample

\*Standard sulphuric acid required

Calculated for C<sub>14</sub>H<sub>29</sub>O<sub>3</sub>N nitrogen 5.4%.

found nitrogen 6.0%.

Physiological Tests.

Since the hydrochloride of the amino ester described above was so deliquescent it was decided to test the physiological activity of the tertiary alcohol. For this purpose a dog weighing between thirty and thirty-five pounds was employed. The alcohol was administered in capsules surrounded by ground meat. The first dose. 1.6 grams, produced light sleep unaccompanied by any ulterior physiological disturbances. Upon the succeeding day another dose was administered, this time 2.4 grams, in the same manner. The effect of this quantity was to produce a much deeper narcosis, lasting about six hours, and from which the animal was aroused with difficulty.

<sup>\*1</sup>c.c. of H2SO4 equal 0.00258 grams of nitrogen.





